


DEEP DIVE

# The race for longevity: How scientists — and industry — are seeking to extend healthy lives



# What's inside

In the early 1990s, biologist Cynthia Kenyon discovered that an alteration to a single gene of a tiny, transparent worm could double the creature's lifespan. Up until that point, most scientists believed that organisms simply wear out over time — an inexorable march toward **molecular entropy**. But Kenyon's findings showed that **aging, age-related illnesses, and even death were processes directed by genetic programs**, raising the tantalizing prospect that they might one day be at least **partly controlled by drugs or therapies**.

“It turned everything upside down,” said Eric Verdin, president of the Buck Institute for Research on Aging — the country's first independent aging research center — and a professor of medicine at the University of California, San Francisco, where Kenyon did her groundbreaking work.

The discovery spawned the field of longevity research, sending scientists chasing after the biochemical secrets that long-lived species like bowhead whales and naked mole rats carry coiled within their cells. Technological innovations arising in subsequent decades — **including genomics, proteomics, and machine learning** — **began to illuminate the mechanisms of aging as well as strategies for short-circuiting them**. Using these insights, researchers have hundreds of times over extended the lives of worms, mice, monkeys, dogs, and other organisms in the lab. These advances helped launch dozens of new companies, all hoping to find a way to extend the amount of time people live free of pain and disease.

Now, 30 years later, the once-fringe field is entering a new phase with the first clinical trials of drugs that are testing the “geroscience hypothesis”— the idea that some **drugs, by altering the trajectory of fundamental processes inside cells, may delay or even prevent the onset of many diseases of old age**.

As longevity research shifts into this era of translation, we spoke with academic experts, pioneers in the field, and executives from more than a dozen companies to identify the most significant challenges surrounding the development of therapies designed to put good years back on people's biological clocks, and to learn how key players are thinking about overcoming those hurdles.

This report first examines the science behind this nascent industry, exploring what we know about the biology of aging and the various types of interventions scientists are studying to help slow or even reverse its corrosive effects. Then, we present the leading companies in the space right now and the status of their drug development efforts. We'll look too, at the vast array of age-related conditions — everything from Alzheimer's disease and cancer to arthritis and glaucoma — that these companies are hoping to treat at their root cause.

Lastly, this report considers the need for such developments. Thanks to vaccines, antibiotics, and other progress fighting pathogens, human life expectancy has nearly doubled over the past century. But a consequence of that success is that the diseases of aging have now surpassed infectious diseases as the leading cause of death. Cancer, Alzheimer's, kidney, and heart disease — these chronic and often debilitating conditions account for the overwhelming majority of health care costs in the developed world, a trend that's accelerating around the globe.

This report is intended for anyone with a strong interest in longevity, including biotech executives, investors, scientists, doctors, policymakers, regulators, and patients and families interested in learning more. Our aim is to make the problems, stakes, and possibilities clear to everyone.



Megan Molteni

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# An aging planet is a sick planet

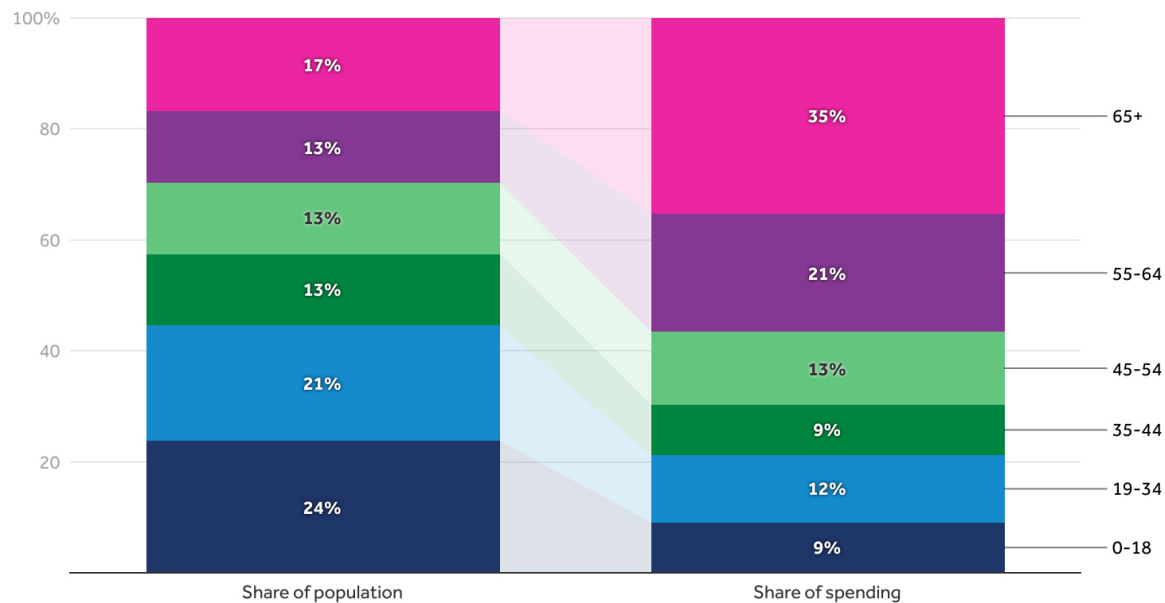
If you were born at the turn of the 20th century in one of today's developed nations, you could expect to live to be about 50 years old, a little less if you were male. Today, average life expectancy has increased to **73 years** in developed nations. But all over the globe more people [are living longer](#).

Data from [the Human Mortality Database](#) suggest these remarkable gains have mostly come from reducing the things that kill people when they're very young — namely malnutrition, poor sanitation and infectious diseases including pneumonia, diarrhea, and malaria. But that doesn't mean that all the years added are good ones. A [recent analysis](#) of the Global Burden of Disease Study found that the proportion of healthy years has held fairly constant over the last few decades. For many people, that means more years spent in poor health.

As of 2018, nearly two-thirds of Americans over the age of 65 had been diagnosed with two or more chronic conditions, including heart disease, stroke, diabetes, cancer, arthritis, and COPD, [according to data from the Centers for Disease Control and Prevention](#). Similar trends have been seen in [Italy](#), [China](#), and most other developed nations. [Researchers estimate](#) that 16%-20% of people's lives are now spent in late-life morbidity, suffering from one or multiple chronic illnesses.

The shift has been costly. Aging populations account for a disproportionate amount of their country's medical expenses. In 2019, Americans over the age of 55 made up 30% of the U.S. population, but accounted for 56% of total health spending, according to [an analysis](#) of data from the Medical Expenditure Panel Survey. And those asymmetries accelerate as people get even older. In the U.S., average Medicare per capita spending more than doubled between 70 years of age and 96 years of age, according to [a 2015 analysis](#) by the Kaiser Family Foundation.

Share of total health spending by age group, 2019



Source: KFF analysis of 2019 Medical Expenditure Panel Survey data

Peterson-KFF  
**Health System Tracker**

And it is projected to get costlier still. Between 2010 and 2050, the number of Americans over 65 will double, the population over 80 will triple, and the number of people in their 90s and 100s will quadruple, according to [a report](#) from the U.S. Census Bureau. As the baby boomer generation continues to age, annual health care spending [is projected to grow to nearly \\$6 trillion](#) — almost 20% of the economy — by 2027.

And yet, funding for research that focuses on the basic biological processes of aging totals less than 1% of the National Institutes of Health budget. “Aging is the climate change of health care,” gerontologists Sean Leng and Brian Kennedy wrote in [a recent analysis](#) of government investment in aging and geroscience.

These impending realities have focused attention on increasing “healthspan” — that is, the number of good years — while minimizing the time spent frail, sick, and in cognitive decline, a goal known as the “compression of morbidity.”

Even a modest extension of the average healthspan could provide a huge economic benefit. According to [one recent estimate](#), delaying the onset of these chronic diseases in every American by even one year would be worth \$38 trillion.

“That’s just mind-blowing,” said Verdin. The promise of intervening in the aging process, he said, isn’t just about shrinking the suffering and enormous expense that accompanies all the many scourges of growing old. It would also usher in a fundamental transformation of the practice of medicine. “We are very good at curing diseases,” Verdin said. “What we’re not good at is preventing disease in the first place. By thinking about aging as a lifelong process that starts around 25 or 30, which you can mitigate with drugs and lifestyle interventions — to me that is an amazing opportunity for us to change medicine from a reactive to a proactive model.”

# What is aging?

For most of human history, the topic of aging fell to philosophers. Plato and Aristotle famously clashed over old age being a plague upon the body and mind or a welcome freedom from earthly desires. But they both agreed that physical decay on the way to death was just an inevitable function of time. That view of aging dominated for centuries, leading scientists to largely ignore and even outright reject it as a subject of study.

“People thought aging was irreversible — basically wear and tear — and that’s boring from a scientific point of view, because what can you really do about it?” said Irina Conboy, a professor of bioengineering at the University of California, Berkeley.

Attitudes began to shift in the 1930s and 40s, starting with a series of studies on mice that found severely restricting their calorie intake could both increase the animals’ lifespans and slow the onset of age-related illnesses. In 1958, Nathan Shock, then chief of the gerontology branch of the National Institutes of Health, created the Baltimore Longitudinal Study of Aging — now the longest-running study of people getting older. The idea was to better understand healthy aging, to help doctors dissociate it from diseases of the elderly. In 1974, the U.S. government established the National Institute on Aging to coordinate and fund similar research in the emerging field.

For most of that time, the science was primarily descriptive — cataloging and quantifying the negative effects of aging. But as recombinant DNA and genome sequencing technologies were introduced in the 90s and 2000s, researchers could really start probing the mechanisms driving it. And as the technologies became more advanced, the boundaries between aging and disease blurred rather than brightened. Today, aging is widely considered to be the greatest risk factor for the leading causes of death.

“Now we have these exponentially improving biomedical research technologies that are all spilling over into lots of different fields, including aging,” said George Church, a biologist at Harvard University and the founder of dozens of biotechnology companies, including a handful focused on aging. “They’re giving us a much more sophisticated understanding of the molecular pathways that are involved.”

Over the last two decades, scientists have identified and mapped these complicated and often interlocking pathways. Out of that effort, nine major hallmarks have emerged, which represent how the field conceptualizes aging today: as relationships between the accumulation of damage and compensatory mechanisms to mitigate that damage.

From the moment we’re born, our bodies are constantly bombarded by chemical and physical assailants both from within and from the outside environment. Alpha particles and other forms of radiation rip through the lipids that confine our cells and break apart DNA. Proteins misfold, organelles deteriorate. We’ve evolved systems to repair all that damage — DNA can be stitched back together, molecules replaced, crippled proteins recycled. But when these systems themselves get damaged, they slowly become less effective.

As scientists identified these age-regulating pathways, they began to illuminate the common origins of the illnesses that afflict the elderly, from cancer to diabetes to dementia. They also opened the door to a previously impossible notion — that the breakdown of age-regulating pathways could be manipulated with drugs and other kinds of therapies.

“By understanding the biology of aging, we believe we’ll be able to tackle a whole series of diseases for which aging is the major risk factor,” said Verdin. “We’ve spent 20 years working on the basic principles of aging in model systems. We’re now at a point where that technology has to be deployed in humans.”

## The nine hallmarks of aging

### **Genomic instability: the accumulation of genetic damage**

Cells have DNA repair systems that deal with damage caused by replication errors, reactive oxygen species, and other physical, chemical, and biological threats. Over time, these systems become less robust, causing DNA changes that affect essential genes and result in dysfunctional cells.

### **Telomere attrition: the cumulative loss of chromosomes' protective caps**

Telomeres are repetitive sequences at the ends of chromosomes that prevent them from fraying or becoming tangled. They can only be replicated by a special enzyme that most mammalian cells lack, so with each cell division, they become slightly shorter. Eventually, they become so short that the cell can no longer divide successfully, and it dies or becomes senescent.

### **Cellular senescence: a stable state of cell cycle arrest**

When cells stop dividing, they enter a zombie-like state where they are still metabolically active but their gene expression changes so they no longer perform their essential functions and instead secrete proinflammatory molecules. The number of senescent cells in some tissues increases with aging, and their accumulation may aggravate damage and accelerate aging.

### **Epigenetic alterations: the accumulation of changes to the structure of DNA**

As organisms age, their chromosomes acquire physical and chemical alterations that impact the expression of genes, including the addition of methyl groups to the DNA strand, modifications to histones — the proteins that bind DNA — and remodeling of chromatin.

### **Loss of proteostasis: when proteins go rogue**

All cells are equipped with an array of quality control mechanisms to ensure that their proteins are correctly folded and to remove, recycle, or degrade any misfolded ones. When these systems falter, damaged proteins accumulate in tissues, leading to several age-related pathologies.

## The nine hallmarks of aging

### **Deregulated nutrient-sensing: when metabolism goes wrong**

Metabolism is the accumulation and breakdown of molecules to maintain the body's balance of energy stores while performing all its necessary functions. As cells age, they get worse at detecting the presence of glucose, insulin, amino acids, and other molecules that tell them whether to free up or capture energy in the body.

### **Mitochondrial dysfunction: when cellular energy factories become less efficient**

Mitochondria metabolize sugars into energy, which is stored in the molecule ATP. As cells age, the electron transport chain that drives production of ATP gets weaker, causing electron leakage and leading to increased production of damaging radical oxygen species.

### **Stem cell exhaustion: the decline in the regenerative potential of tissues**

Stem cells are the starting material from which all other cells are generated. Aging causes a decrease in the cell-cycle activity of stem cells — they don't renew themselves as frequently or produce as many of the specialized cells that make up tissues.

### **Altered intercellular communication: mixed signals**

Cells use all kinds of chemicals to speak to one another as they work in concert to keep a body running smoothly. Aging causes these communication networks to go haywire — getting too much of one signal or not enough of another. This often leads to a constant state of alarm, known as “inflammaging,” which can set off cascades of other deleterious change throughout the body.

# The story of metformin and the tragedy of the TAME trial

For centuries, physicians in medieval Europe treated everything from pocks and plague to worms and insect stings with extracts of goat's rue — a bushy plant sporting tiered towers of downturned white flowers. In the late 1800s, chemists isolated its active ingredients, including one that scientists later discovered could lower blood sugar. In 1994, the Food and Drug Administration approved a slightly modified version of that compound, called metformin, as a treatment for diabetes. Since then, it has been prescribed to hundreds of millions of people around the world.

Beginning in the late 90s, researchers began comparing the health of people on metformin to those taking other diabetes medications. Over and over [they found](#) that the metformin-takers had fewer heart attacks, got cancer less frequently, were less likely to suffer from dementia and Alzheimer's, and in general just tended to live longer, healthier lives. It also turned out to be very safe, with few, generally mild, side effects. And it's dirt cheap: just six cents per dose.

That made it the ideal candidate for Nir Barzilai's big plan.

As the head of the Institute for Aging Research at the Albert Einstein College of Medicine, Barzilai had been leading the charge to test the idea of using drugs to extend human healthspan. In 2013, he and two other researchers got a grant from the National Institutes of Aging to develop a roadmap to conduct, for the first time in history, a clinical trial that targets aging. The biggest obstacle they had to find a way around was the FDA.

The federal regulator adheres to a “one disease, one drug” model of approval. And because the agency does not recognize aging as a disease, there’s no path forward for a drug to treat it. And even if there was, it’s impractical to do a lifespan study — it would take decades and be astronomically expensive.

The solution then, would be to use biomarkers as a proxy. Statins, for example, are a class of drugs the FDA approved to prevent heart attacks. But clinical trials of statins didn’t test that explicitly because it would have taken too long. Instead, they tested for changes to blood pressure, a well-defined predictor of heart attacks. There are, however, no standard accepted biomarkers for aging, although scientists are actively searching for them.

So Barzilai’s plan was to launch a new kind of gold-standard trial, designed to prove that the onset of multiple chronic diseases, or comorbidities, associated with aging can be delayed by a single drug: metformin. The ambitious effort aimed to track 3,000 elderly people over five years to see if the medicine could hold off cardiovascular disease, cancer, and cognitive decline, along with mortality.

“There’s nothing in that clinical trial that hasn’t already been shown before with metformin,” said Barzilai. “We are just trying to package it all up and call it aging so the FDA will approve this for aging.”

In 2015, he and a group of academics from more than a dozen top-tier universities met with the FDA to get its blessing for their Targeted Aging with Metformin, or TAME, trial. And to many people’s surprise, the agency agreed.

All that was left was funding it. Because metformin is a generic drug from which no one could make any money, the trial’s sponsor wouldn’t be a pharmaceutical company, but a nonprofit called the American Federation for Aging Research. A trial of the scale researchers were proposing would cost between \$30 million and \$50 million.

The National Institutes of Health offered up just a small portion, about \$9 million, toward the difficult but important task of screening for the best biomarkers for assessing if the aging process is actually being slowed.

The rest of the money, Barzilai was convinced, could be raised from philanthropists. But despite interest from several people — at one point, Barzilai said, the Israeli-American businessman Adam Neumann offered to pay for it all, before his WeWork empire evaporated — the required funds never materialized.

“I’m on the record saying I’m pretty sure it will start this year, for the last seven years,” said Barzilai. “I have no credibility anymore. It’s just incredibly frustrating. But it’s going to happen, because it has to happen.”

“The metformin story is a particularly tragic one,” said James Peyer, co-founder and CEO of Cambrian Biopharma, a four-year-old company that has raised \$160 million with its “hub and spoke” approach to develop more than a dozen different drug candidates aimed at diseases of aging.

Like many other industry players and academics STAT spoke with, Peyer believes the TAME trial could be a paradigm-shifting pilot experiment and create a framework for biotechnology companies to follow in the future. “If we had more knowledge from a philanthropically-run trial with a really safe molecule, that would be a boon for the whole field. It would be huge. But it’s been more than six years since the FDA gave a green light. It should almost be done by now.”

# What therapies are in clinical development?

Aging research has identified hundreds, if not thousands of promising compounds capable of turning back the biological clocks of flies, worms, and mice. Dozens of companies are trying to translate that science into medicines to slow down or reverse the aging process in humans, and they're hoping to treat or prevent the progression of age-related conditions as varied as macular degeneration, Alzheimer's disease, cancer, and even infertility.

But "anti-aging" drugs aren't yet available, except for participants of clinical trials. No company has successfully made it through the FDA's regulatory pathway. Like all new medicines, drugs that target aging have to be tested in animals before they go into humans, and then only about 1 in 10 are ever cleared as safe and effective.

Going after aging directly has proven particularly difficult for drug developers. Many have failed in the past. And the current crop of biotech upstarts are undercapitalized, making their bets even riskier for investors.

Still, trials are underway, and if successful, a handful of companies could be filing for approval within the next five to 10 years.

# Cellular senescence

Cellular senescence — a zombie-like state of existence [first described](#) in 1961 by Leonard Hayflick at the University of California, San Francisco — has drawn some of the most sustained interest from anti-aging drug companies thus far.

As damage accumulates in aging cells, they stop dividing so they don't help replenish tissues. They're dysfunctional but they refuse to die. For decades, scientists believed this process to be a mostly innocuous defense mechanism against cancer.

But [work by Jan van Deursen](#) at the Mayo Clinic and [Judith Campisi at the Buck Institute](#) in the early 2000s found that senescent cells actually fuel the aging process by secreting a cocktail of toxic molecules that cause inflammation and damage surrounding tissues.

By 2011, van Deursen's lab [had shown](#) that purging mice of senescent cells through genetic engineering delayed the onset of all kinds of age-related tissue degeneration. He and Campisi were quickly recruited to found a new company called Unity Biotechnology formed to find drug compounds that could do the same thing in people. Unity was first, but today there are [more than a dozen startups](#) pursuing senolytic strategies, including senescent cell destruction, prevention, and reversal.

“It's incredible how fast it's moving,” said James Kirkland, a geriatrician at the Mayo Clinic who collaborated with van Deursen on the 2011 study that launched the field of senolytics.

Kirkland heads up something called the [Translational Geroscience Network](#) — a National Institute on Aging-funded effort to repurpose and test in parallel a slate of already approved drugs to see how well they can target fundamental aging processes and treat age-related conditions.

In 2016, Kirkland launched his first clinical trial with dasatinib and quercetin, two cancer drugs commonly given to survivors of hematopoietic stem cell transplants. The regimen proved safe, and is now being tested by academic researchers in seven clinical trials, evaluating its impact on frailty, immune health, Alzheimer's disease, and age-related diseases of the lungs and kidneys. Trials with another senolytic called fisetin — an anti-inflammatory compound found in strawberries and sold as a health supplement — are also ongoing.

“It's beginning to look like there might be a glimmer that these geroscience interventions might add to existing interventions,” said Kirkland. “I'm a conservative physician; I've gone from thinking there's a 0.001% chance these drugs will work to maybe a 20% chance. But I have to see the data before I believe any of it.”

These academic trials likely offer the best first chance at showing the concept of senolytics is viable in human patients. But the compounds being evaluated are far from ideal and carry the risk of off-target toxicity. That's why companies are developing drugs designed to modulate senescence in specific tissues with hopes they'll have even more pronounced benefits.

Unity, the only one to generate clinical data so far, is by far the biggest player, but other promising approaches are also being developed by Recursion Pharmaceuticals and Deciduous Therapeutics.

## UNITY BIOTECHNOLOGY

Launched in 2011, Unity Biotechnology is among the oldest companies working on anti-aging drugs. Backed by Arch Venture Partners as well as Silicon Valley heavyweights Peter Thiel and Jeff Bezos, the company raised nearly \$300 million before its IPO in 2018.

Its founder, Ned David, [hoped the company](#) would eventually develop drugs to treat all the diseases that can come from growing old — starting with its lead candidate UBX0101, for osteoarthritis. Initial data for biotech’s first shot at senolytics [proved more promising](#) than most biotech analysts expected.

But Unity took a hard hit in August 2020 when its Phase 2 clinical trial for UBX0101 suffered [a high-profile failure](#) that threw a pall over the emerging senolytic field.

In a study of 183 patients with moderate to severe osteoarthritis, only those who received the highest dose of UBX0101 saw a slight improvement in knee pain after 12 weeks. The other two doses didn’t yield any improvements compared to a placebo.

Unity’s stock plunged more than 60% on the news. Rather than try again, the company swiftly abandoned its experimental drug, laying off nearly a third of its staff a month later. David stepped down at the end of the year.

“When I look back at it, there was one big area of translational uncertainty that accompanied that program into the clinic,” said Anirvan Ghosh, a former Biogen executive who took over as Unity CEO in March 2022. “Most of the preclinical data came from an ACL injury model, where you do get accumulation of senescent cells, but translating that to a chronic state of osteoarthritis was too big a job.”

Believing the strategy of senolytics is still strong, Ghosh has pivoted the company away from musculoskeletal targets and towards ophthalmologic and neurologic indications. And once again, the company is on the precipice of a potentially game-changing readout.

In July 2021 the company announced positive results from the Phase 1 study of its vascular eye disease program: UBX1325. A small-molecule inhibitor of Bcl-xL, the drug targets senescent cells in the vasculature of the eye, and showed improvements in vision lasting up to six months following a single intra-eye injection.

The drug is now being tested in two Phase 2 studies — one in diabetic macular edema (which should have initial results by mid-2022) and one in macular degeneration (with a readout expected by the end of 2022 or early 2023).

“We’re used to taking pills every day or getting an infusion every month, if it’s a biologic, but we don’t have a class of drugs where you have a single intervention and then you come back and take it again six months or a year from now,” said Ghoshan. “At this point it’s still hard to fully believe, because we don’t have anything like that. But fundamentally, there is nothing in the science that will prevent it from happening.”

## **RECURSION PHARMACEUTICALS**

This Salt Lake City-based company was founded in 2013, and raised more than \$436 million before going public in 2021. It uses machine learning to hunt for new drug targets among massive datasets of cell features and functions, many of which Recursion produces in-house.

It has two candidates in late-stage clinical trials — a superoxide scavenging small molecule drug to treat abnormal blood vessel development in the brain, and a histone deacetylase inhibitor for the treatment of neurofibromatosis type 2, a genetic condition that causes tumors of the central nervous system.

Neither of those are anti-aging programs. But starting in 2016, Recursion began developing profiles of senescent cells across a variety of human cell types with nearly \$2 million in support from the National Institutes of Aging. By combining this dataset with others, the company identified REC-4249, a small molecule senolytic it is now evaluating in preclinical studies as a potential treatment for connective tissue disease scleroderma.

This degenerative disorder is characterized by hardening connective tissues, and most often occurs in older people. However, it's unclear when human trials of REC-4249 might begin; for now, the company is focused more firmly on its neurological and fibrosis programs.

## **DECIDUOUS THERAPEUTICS**

One of the newest entrants to the senolytics space, Deciduous Therapeutics, came out of stealth in 2021 with backing from 8VC, CRV, and the Longevity Fund.

Rather than using a small molecule to clear senescent cells, the company is developing compounds that train immune cells to identify and remove senescent cells. The approach comes out of the University of California, San Francisco, lab of scientific co-founder Anil Bhushan, who discovered in 2019 that senescence triggered the onset of type 1 diabetes in mice.

More recently, Bhushan's lab found that as animals age, the immune cells responsible for clearing senescent cells — invariant natural killer, or iNKT cells — get turned off. By turning them back on, they showed iNKTs selectively removed senescent cells in obese mice, stabilizing their metabolism, and in a mouse model for lung disease, which caused the animals to live longer, healthier lives.

“The issue in the field has always been ‘what is the actual immune system process behind senescence clearing?’” Deciduous CEO Robin Mansukhani told STAT in 2021. “And I feel like we’ve uncovered that.”

The company expects to file its first investigational new drug application to start human testing by the end of 2023, likely for a metabolic disease or fibrotic lung disorder.

# Deregulated nutrient-sensing

As far back as the 1930s and 40s, researchers had shown that severely restricting the calories mice consume led them to live longer lives. But it would take more than 60 years to begin to map out the specific molecular pathways linking metabolic alterations with aging. In 1994, scientists from Harvard, Johns Hopkins, and the Mayo Clinic independently discovered a master switch for controlling these pathways: the mTOR protein kinase.

A few years later, a molecular biologist named Dave Sharp at the University of Texas Health Science Center suggested that mTOR might be the key to the longevity effects of calorie restriction because of its role connecting the availability of nutrients in the environment with control over most of a cell's metabolic processes.

Inhibiting mTOR via genetic manipulation lengthened the lives of worms and fruit flies. [Studies had also shown](#) that in yeast, the longevity starvation effect could be mimicked by inhibiting TOR with rapamycin — a compound isolated from bacteria found on the island of Rapa Nui in the 70s, later found to be a powerful suppressor of cell growth and approved by the FDA for reducing organ transplant rejection.

In 2009, [Sharp and his collaborators reported](#) that feeding rapamycin to old mice significantly extended their lives — the first time a pharmacological intervention increased life span in a mammal. Since that breakthrough, rapamycin has [also been shown](#) to stave off or improve a diverse range of conditions including arthritis, blindness, cardiac disease, and Alzheimer's disease in mice, suggesting mTOR inhibitors could be promising treatments for a broad spectrum of age-related diseases.

Two analogs of rapamycin, sold under the names Afinitor and Torisel, have also been approved for treating cancer.

Afinitor is made by Novartis, which in 2014 recruited an infectious disease researcher named Joan Mannick to lead its new Indications Discovery Unit, tasked with developing medicines for areas outside the traditional pharma silos. Mannick wanted to work on aging. Although rapamycin and rapalogs were best known for their immunosuppressive effects, [studies in mice](#) had also shown that the drugs could boost age-related declines in immune function.

Mannick wanted to see if a similar effect could be achieved in humans. As people age, their bodies produce fewer of the kinds of immune cells that help recognize and fight off invading pathogens. That means vaccines tend to be less effective the older you are. Mannick and her colleagues at Novartis initiated a study in older healthy adults with one of the company's rapalogs, to see if it could function as an immune-boosting primer before vaccination with the influenza vaccine.

They found the combo improved responses to the shot by about 20%. They also noticed people had far fewer respiratory tract infections of all kinds, not just the flu, over the following year.

“It was really interesting, because when we looked at the gene expression pathways in those people, the only ones that significantly changed were all critical antiviral genes getting upregulated,” said Mannick.

That insight led to the founding of resTORbio. And although that company is no longer focused on anti-aging drugs, following a Phase 3 flop, it's included here, along with two others targeting the mTOR pathway: Tornado Therapeutics and Navitor Pharmaceuticals.

## RESTORBIO

Based in Boston, this company spun out from Novartis in 2017 with Mannick as co-founder and CMO. The idea was to show its licensed drug, RTB101, could improve the function of the aging immune system.

In a Phase 2 clinical trial, it looked like that might be possible. The company [published](#) positive results in Science Translational Medicine in 2018, showing patients who received RTB101 were diagnosed with up to 30% fewer respiratory infections over the following year.

But a Phase 3 trial, launched in 2019, failed to show the desired effect. A possible contributing factor was the FDA's decision to require resTORbio to change its endpoint from a lab-confirmed infection to self-reported symptoms, fearing that participants wouldn't submit to regular nose-swabbing.

"It was heartbreaking to have that trial fail because so much of the field was counting on this to maybe be the big breakthrough," Mannick said. "But I think in retrospect, as we go into these new indications for aging, we're going into the unknown and we just have to try and learn and iterate."

In April 2020, resTORbio merged with Adicet Bio, taking the company's name and focus on CAR-T cell cancer treatments.

Following the merger, RTB101 was returned to Novartis, which declined to comment on its future development plans. The company has since sunset its Indications Discovery Unit.

## **TORNADO THERAPEUTICS**

While Mannick was at reSTORbio, a team of scientists at Novartis continued to push forward a program she had been a part of there to produce new rapalog chemistries with more favorable safety profiles. Ultimately, they came up with 82 novel compounds that also target the mTOR pathway.

In February, Tornado Therapeutics, a new Cambrian Biopharma partner company helmed by Mannick, licensed this next generation of mTOR inhibitors from Novartis for further development.

Tornado hasn't disclosed its lead indications yet, but Mannick said there will still be a focus on improving immune function in older adults. The company hopes to launch clinical trials by the end of 2023.

## NAVITOR PHARMACEUTICALS

Based in Cambridge, Massachusetts, this company launched in 2014 with \$25 million in initial financing from Polaris Partners, Atlas Venture, and The Longevity Fund. Navitor planned to tackle a wide range of diseases, including metabolic, neurodegenerative, and autoimmune disorders with technology developed in the MIT lab of its scientific founder, David M. Sabatini.

Sabatini was among the first researchers to isolate the mTOR protein, and subsequently made a series of important discoveries about its role in nutrient signaling. In 2021, Sabatini was forced out of the Whitehead Institute, and later resigned from MIT, after a probe found he violated the institution's sexual harassment policies. He is no longer involved with the company.

Navitor initially focused on drugs to treat depression, muscle wasting, and age-related declines in cognition. NV-5138, its mTOR activator, is now in Phase 2 trials for treatment-resistant depression, in partnership with Supernus Pharmaceuticals.

A spin-out company called Anakuria, with a Phase 1-ready mTOR inhibitor for treating autosomal dominant polycystic kidney disease, was acquired by Janssen in February.

Following the sale, Navitor reduced staff and is now primarily focusing on co-developing NV-5138 with Supernus. While the partnership has dropped muscle wasting as a potential indication, Navitor CEO Tom Hughes said that they're keeping age-related cognition decline on the table for potential further development down the road.

## Altered intercellular communication

Cells are constantly communicating with each other through chemical signals. And blood is the body's information superhighway. As cells age, they become less adept at reading and reacting to their environments and those communication networks break down, leading to all kinds of problems.

In 2005, Conboy, her husband Michael, and their team at UC Berkeley published a landmark paper in *Nature*, showing that many of those problems could be ameliorated — at least in mice — by connecting the circulatory systems of old animals to young ones, in a procedure called parabiosis. Blood from the young mice restored normal signaling in the old ones, leading to rejuvenated tissues, stronger hearts, and sharper minds.

Over the subsequent decades, more of these sorts of studies have offered provocative clues that certain hallmarks of aging can be reversed by young blood. Such research fueled a rise in dubious plasma transfusion startups, causing the FDA to issue a stern public warning in 2019 that the procedure provides no known clinical benefit.

But during that same time, serious scientists and companies began searching for the most potent chemical drivers of those effects, with aims on bottling them up into a drug the FDA might approve.

One of the pioneers of this effort is Tony Wyss-Coray, a neuroscientist at Stanford University. In a 2014 *Nature* paper, his lab demonstrated that infusions of blood from young mice increased neuron growth and improved memory in old mice. This work launched a small company, Alkahest, to test whether transfusions of plasma from young people might help treat Alzheimer's disease. Results from the first clinical trial were lackluster.

And other influential studies suggesting individual components of young blood could increase muscle strength, heart function, and cognition also have proven difficult to replicate.

More recent research from the Conboys, however, has offered a potential window into why many such promising leads hit dead-ends. In two studies published in 2020, they showed that merely diluting plasma with saline or albumin produced similarly rejuvenating effects. “For years everybody was running after the young factors,” said Conboy. “Now the direction has shifted toward looking at which old factors need to be neutralized.”

## **ALKAHEST**

This Bay Area-based company initially helmed by Genentech alums began as a whole plasma infusion company focused on neurodegenerative disease.

But mixed results from its first safety study in Alzheimer’s patients inspired a pivot toward finding and testing different plasma protein cocktails for a wider range of indications, including retinal diseases, immune disorders, and other age-related diseases involving systemic inflammation.

The company’s lead drug, GRF-6019, is a mix of about 400 different types of plasma proteins. In a 47-person [Phase 2 study](#) published in 2021, patients with mild to moderate Alzheimer’s maintained or improved their level of cognition for six months. A Phase 2 study of the drug is now underway in severe Alzheimer’s. A different plasma protein cocktail, GRF-6021, is also in Phase 2 studies for treating Parkinson’s disease.

In 2020, Alkahest was acquired by Grifols, a large Barcelona-based plasma processing company. It paid \$146 million for the shares it didn’t already own — just over 50% of Alkahest’s stock.

The company is also developing an oral CCR3 inhibitor it acquired from Boehringer-Ingelheim. It works by blocking the binding of eotaxin, a protein that triggers inflammation and that is found in high levels in the blood of older people. That drug is currently in Phase 2 trials for the treatment of age-related macular degeneration and Parkinson's disease. Alkahest has not disclosed when readouts can be expected.

# Following the (big) data

Not all the promising shots on goal fit so neatly into the established hallmarks of aging. Which isn't surprising — many signaling pathways implicated in diseases of aging ping back and forth between those fundamental processes. And those connections are often best revealed by big data approaches.

Here's a look at two leading companies doing that kind of cross-cutting work: BioAge Labs and Insilico Medicine.

## BIOAGE LABS

Backed by Silicon Valley venture capital heavyweight Andreessen Horowitz, BioAge Labs launched in 2017 with aims of building a machine learning platform to address aging's biomarker problem.

Led by founder and CEO Kristen Fortney — formerly a bioinformatician at Stanford's Center on Longevity — BioAge has been combining lab tests of anti-aging compounds in mice with datasets gathered from long-lived individuals in Estonia, the U.K., and elsewhere, to develop reliable chemical predictors of mortality.

In the process, the company identified drugs already in clinical development that could alter those molecular causes of aging. During the pandemic, BioAge began building out its clinical team to be able to test those drugs for age-related indications. So far, it has acquired three assets it's developing for two initial programs: muscle frailty and immune aging.

“Our datasets point to several dozen different pathways that matter for longevity,” said Fortney. “We decided to focus first on the pathways closest to translation.”

One thing those datasets revealed is that as people aged, some of them produced less apelin, a blood peptide involved in regulating many physiological processes including blood pressure and muscle growth and repair. Those people were more likely to be frail and not live as long as people with higher levels of apelin in their blood. [In a 2018 Nature Medicine report](#), a research team in France found that boosting apelin levels in mice reversed signs of sarcopenia.

A few years later, BioAge signed a deal with Amgen to license BGE-105, an APJ agonist that mimics production of apelin. In 2022, the company began a Phase 1 trial of the drug in healthy adults. It plans to proceed with a Phase 2 in patients with hospitalization-related muscle atrophy.

BGE-175, an oral drug licensed from Taisho Pharmaceutical, targets a prostaglandin signaling pathway that becomes dysregulated as people age, leading to too many of some immune cells and not enough of others. In [studies of mice](#) published in Nature, BioAge and its academic collaborators showed that daily doses of BGE-175 protected aged mice from SARS-CoV-2. The company is currently conducting a Phase 2 trial of the drug in elderly Covid-19 patients in Brazil, Argentina, and the U.S.

In early 2021, BioAge moved BGE-117, which activates hypoxia-inducible factor (HIF) — a key regulator of how cells sense and respond to low levels of oxygen — into Phase 2 trials in age-related anemia. The drug had originally been developed by Taisho Pharmaceutical for increasing erythropoietin levels in patients with chronic kidney disease, but BioAge's algorithms unearthed a link between higher HIF activity and higher physical and cognitive function, suggesting it had the potential to treat multiple diseases of aging beyond anemia.

## INSILICO MEDICINE

Insilico isn't an anti-aging biotech company so much as an artificial intelligence drug discovery startup with a focus on age-related diseases.

Founded in 2014, the California-based company has raised more than \$380 million in private financing, which it is using to develop its own pipeline of [AI-discovered and designed drugs](#), starting with ISM001-055 for idiopathic pulmonary fibrosis — a chronic lung disease that primarily occurs in older adults.

ISM001-055 doesn't work by clearing senescent cells, but it does target “a regulator of several key pathways implicated in aging and disease,” including extracellular matrix stiffness, genomic instability, and cellular senescence, Insilico CEO Alex Zhavoronkov told STAT via email. That target, which the company has not yet disclosed, was discovered by aiming Insilico's AI platform, PandaOmics, at identifying molecules involved both in lung tissue scarring and pathways of aging.

Fibrosis is characterized by the accumulation of scar tissue as the result of injury or aging, rather than the regeneration of healthy lung cells, which leads to a stiffening and dysfunction of tissues. It's related to a number of hallmarks of aging but is not yet considered one on its own, which Zhavoronkov thinks is a mistake. “I think it should be named the senofibrosis or fibrosenescence hallmark,” he said.

Insilico tested ISM001-055 in eight healthy volunteers in a Phase 0 exploratory trial in Australia last year. In February, the company announced it had begun a [Phase 1 trial](#) with 80 healthy volunteers to determine dosage recommendations for potential Phase 2 trials, which Insilico hopes to initiate in the first half of 2023, “if the stars align,” said Zhavoronkov.

# Moonshots

Beyond this rapidly expanding crop of more traditional biotech companies chipping away at diseases of aging, there are three exceptionally well-funded outfits with even more ambitious aims: Calico, Altos Labs, and Hevolution.

## CALICO

In 2014, then-Google CEO Larry Page unveiled the tech giant's next big bet: Calico, an independent venture focused on extending the human lifespan. Led by Art Levinson, the former CEO of Genentech, and with Cynthia Kenyon as VP of Aging Research, the company's mission is to “develop life-enhancing therapies for people with age-related diseases.”

Its first big move was to build a drug research and development facility in South San Francisco under a \$1.5 billion partnership with the pharmaceutical company AbbVie. Since then, the companies have jointly committed another \$2 billion each — in 2018 and in 2021 — giving it an incredibly long runway to pursue aging-related research and drug development.

The partnership has two programs — in immuno-oncology and neurodegeneration — that are just now entering Phase 1 clinical trials. ABBV-CLS-579 and ABBV-CLOS-484 are both checkpoint inhibitors, which block a protein called PTPN2 involved in stopping the immune system from attacking certain types of cancer cells.

In February, Calico announced its plans to begin a study later this year in ALS patients with ABBV-CLS-7262 — a small molecule drug that targets a key regulator of cellular stress in the brain, which the company licensed from the lab of Peter Walter at UCSF.

Calico has an additional 20 programs in preclinical development, ranging from testing drug candidates in mice to studying the basic biology of aging in long-lived species. (Calico maintains the largest colony of naked mole rats in the world.)

Although it has published more than 50 journal articles since its launch, some of which have drawn attention from the field, Calico has yet to produce a blockbuster breakthrough. It has also lost several big-banner hires, including Hal Barron, who left his post as president for research and development for GlaxoSmithKline (and this year moved to Altos), and Daphne Koller, Calico's top AI researcher who left to launch her own drug discovery company, Insitro.

Calico rarely grants interviews, but in statements, it has defended its deliberate approach. “We believe that at the root of every great advance in medicine is a deep understanding of the biology that underlies a specific disease pathway,” [Levinson said in February](#). “The quest for this depth of understanding has been our primary focus.”

## ALTOS LABS

Altos Labs burst onto the scene in early 2022 with \$3 billion — perhaps the largest amount of capital ever raised for a biotech startup — and plans to beat back diseases of aging.

Altos is led by serial biotech entrepreneur Richard Krausner; Hans Bishop, who served as CEO of Juno Biotechnology and Grail; and Hal Barron, formerly the chief scientific officer of GlaxoSmithKline.

The company was founded to advance the science of partial reprogramming. It's a way to reset an aging cell's epigenetic code — the complex set of chemical tags that toggle its genes on or off.

In 2012, Shinya Yamanaka won the Nobel Prize in Physiology or Medicine for his work showing that a few combinations of transcription factors could erase those tags, making a cell forget it was ever a neuron or skin cell and reverting it back to a more primitive state. The technique has been widely adopted to manufacture stem cells. Partial reprogramming doesn't roll back a cell's epigenetic clock that far, but it does remove changes to a cell's chromosomes that cause it to function less efficiently as it gets older.

The method was first demonstrated in [a 2016 Cell report](#) by a team led by Juan Carlos Izpisua Belmonte at the Salk Institute. The mice they partially reprogrammed seemed to age in reverse — becoming more physically robust with kidneys that filtered better and hearts that pumped harder. They also lived 30% longer than their littermates.

[Krausner told STAT](#) the idea for Altos came out of informally surveying friends and colleagues about the biggest problems in biology. Out of those conversations he became “just blown away with this new science of cell health and reprogramming.”

The long-term goal is to eventually develop therapies. But for now, basic science is firmly on the front burner for Altos, which is organizing itself like a bi-coastal Bell Laboratories, but for biology.

The company is now running three Altos Institutes of Science, out of San Diego, the San Francisco Bay Area, and Cambridge, U.K., headed by Izpisua Belmonte, Peter Walter (UCSF), and Wolf Reik (Cambridge University), respectively.

With big names and deep pockets, Altos is poised to perhaps make the most dramatic dents on diseases of the old, but it could be a long time before they materialize.

## HEVOLUTION

The kingdom of Saudi Arabia is the latest entrant to make a big bet on treatments to extend healthspan, and it might turn out to be the biggest one yet. In summer 2022, the Saudi royal family went public with the Hevolution Foundation, a nonprofit organization it chartered by royal decree in 2018. It plans to spend up to \$1 billion a year sponsoring basic research on the biology of aging and investing in life sciences startups, the fund's CEO, Mehmood Khan, a former Mayo endocrinologist and PepsiCo executive, told [MIT Technology Review](#).

Also on board as chief science officer is Felipe Sierra, a former division head at the National Institute on Aging. For comparison, that agency has an annual budget of about \$325 million.

Hevolution has so far been quiet, at least in public, about what research and drug studies it intends to back. And given [the allegations U.S. intelligence agencies have made](#) accusing the Saudi Crown Prince Mohammed bin Salman of orchestrating the killing of American journalist Jamal Khashoggi, there are likely to be scientists in the field unwilling to avail themselves of the windfall.

But Barzilai isn't one of them. He's hoping Hevolution will help him fund the long-awaited TAME trial, and even went so far as to tell an audience in April that a deal was in the works. However, a spokesperson for the foundation disputed that account, telling STAT it has "not yet made any decisions" about funding specific projects or ventures.

# A complicated regulatory environment

Whether or not old age is considered a plague upon the body or a normal part of biology is not just a question for the philosophers, but one that has real implications for developing medicines.

Every few years, the World Health Organization publishes the International Classification of Diseases, a manual used to track illnesses around the world that's also used for insurance coding purposes. [The latest issue](#), which went into effect on Jan. 1, 2022, includes around 17,000 codes for all the things that people get sick and die from, including an extension code for “ageing-related” diseases for conditions that worsen as people get older. But aging itself is not one of them.

That makes it difficult to take science that slows or reverses aging and wrap it into a product that can easily win FDA approval. To apply to run a trial, drug sponsors must include an “Indication for Use” section that describes what the drug does and the clinical condition it is intended to treat. The FDA has never allowed such a drug on the market, because aging hasn't been designated as a condition requiring treatment.

For this reason, most longevity-focused biotechnology companies are instead initially designing medicines targeted at specific diseases, the risks of which go up as people age. Their roadmaps involve first proving those drugs can work safely and effectively to treat acute conditions, before eventually testing the same interventions in prospective clinical trials with healthy people for the prevention of diseases like cancer and Alzheimer's.

“I think what’s going to impact patients in a preventative, longevity way much, much earlier are prosaic things — small molecules, biologics that can be manufactured at large scale — where we can clearly understand a solid safety profile and can then be pivoted from rare or chronic disease X into prevention,” said Peyer of Cambrian Biopharma.

He said the sector is looking to model what happened with statins — the cholesterol-reducing drugs that [an estimated 173 million people](#) around the world take daily. The first statin was approved in 1987 for a narrow set of individuals, following clinical trials that tested the drug’s effectiveness in patients with rare inherited forms of high cholesterol. Over time, researchers were able to show it lowered the risk of heart attack and stroke, and its use was expanded to a more general population.

“So we’re looking at things that are either dealing with a chronic disease and making it progressively better, or redefining a composite biomarker like high cholesterol as a pre-disease state that you can then treat and prevent someone from moving to sickness,” Peyer said.

The hope is that as scientists tease apart how getting older raises the risks of numerous diseases, aging itself might be seen as a treatable condition, in the same way a doctor would treat high blood pressure or a vitamin deficiency.

“The FDA recognizes that there is interest in developing drugs with the potential to target mechanisms of aging,” an FDA spokesperson told STAT in an email. “The FDA engages with sponsors of such products to provide advice regarding the design of potential development programs that may generate sufficient data to support an approval. Whether a drug could be approved for ‘aging’ as opposed to a more-specific indication would, in part, depend on the evidence generated.”

Aging mechanisms that operate over someone’s lifespan might only produce evidence of clinical effects after decades.

A gold-standard trial to see if a drug makes people live longer, healthier lives could easily run 50 years and cost many hundreds of millions of dollars.

“It’s just not feasible,” said Steve Horvath, a geneticist at the University of California, Los Angeles. “Therefore, the field is desperate to have biomarkers where you do the same sort of clinical trial but only for one or two years, and then you measure something to see if it improved.”

Horvath has been a pioneer in developing such biomarkers. In the early 2000s, he demonstrated for the first time that organisms have epigenetic clocks — patterns of DNA methylation that closely track the aging process. Since then his lab has developed newer, more predictive clocks, like PhenoAge and GrimAge (named for the Grim Reaper), whose usefulness in clinical trials are not yet proven, but look promising.

The FDA has, at times, accepted surrogate endpoints as predictors of future clinical effects — most recently in its [controversial approval of the Alzheimer’s drug Aduhelm](#). The agency is working with academics and industry to evaluate various biomarkers that might one day become a standard for aging, as blood pressure is for hypertension and risk of heart attack and stroke.

“A new push is on to develop something the FDA could accept, something we’re calling gerodiagnostics,” said the Mayo Clinic’s Kirkland. He describes this as panels of blood, urine, and saliva tests combined with EKGs, physical examinations, imaging, and epigenetic clocks among other measurables. “Some of the biggest pharma companies that have invested in this and certain academic groups, we’re all very interested in setting up something like the internet protocol that everybody uses — something that tells us which fundamental aging processes are operative in a person, which ones to target, when to intervene, and if there’s a response to that intervention.”

The trials in Kirkland's Translational Geroscience Network are all coordinating to collect lots of that kind of data, as are trials being planned by Cambrian's partner companies. Horvath has also started a nonprofit to help academics and early-stage drug developers add epigenetic clocks to their trials as secondary endpoints.

Recently, more coordinated efforts to smooth a path for gerotherapeutics amid the regulatory uncertainties have emerged. In March 2022, the Alliance for Longevity Initiatives launched in the U.S., following the formation the previous year of the Longevity Biotechnology Association in the United Kingdom. Both lobbying organizations aim to educate lawmakers and set standards and best practices for the nascent industry.

"It's a reflection of the difficulties that lie ahead and trying to organize in a way that will facilitate not only the clinical trials but also the dissemination of all this biology," said Verdin, who is a founding member of both groups.

# The pivotal decade ahead

Tales of time-reversing elixirs flowed through human civilizations well before Juan Ponce de León set out to find the Fountain of Youth in the late 1400s. And the mythic spring of eternal hope has sprung, eternally, down through the centuries, taking on more modern incarnations like supplements, hormone treatments, and stem cell injections.

In the U.S., the FDA's lack of regulation of practices or products designed to address aging has meant that treatments that purport to fight aging have not historically been vetted. By the year 2000, anti-aging products had become a multimillion-dollar business, even as those hawking them often misrepresented the science upon which they were based, if they were based on science at all.

The scientists and drug developers working on what they hope will be the first generation of medical interventions that modify the underlying processes of aging acknowledge that this long, fraught history of science at the fringe is doing them no favors. But they also insist that this time, it might actually be different.

“All this anti-aging noise hasn't helped the reputation of the field,” said Barzilai. “There are a lot of snake oil salesmen and charlatans telling people they'll live forever. That's not what we're doing. We're targeting aging to delay a lot of age-related diseases.”

Supplements and shady stem cell clinics aside, longevity biotech has also been littered with failures that hit closer to home: Unity's osteoarthritis drug, reSTOR's respiratory infection flop, and before that there was Samumed and Sitris Pharmaceuticals.

In 2008, GlaxoSmithKline purchased Sitris for a staggering \$720 million only to find out a few years later that the calorie restriction-mimicking compounds it had developed didn't actually target the sirtuin pathway, another regulator of metabolism long-linked to longevity.

Then came Samumed, which launched out of stealth in 2016 with a war chest of \$220 million and promised its drugs could reverse aging in specific organ systems — regenerating cartilage in creaky knees, removing scarring in the lungs, restoring hair to bald pates — by modifying a downstream signaling pathway from mTOR. In 2021, the company rebranded itself as Biosplice Therapeutics, axed its lead program for male pattern baldness, and laid off more than 40 workers.

The lesson, many say, is that it's easy to raise money if you're going after longevity. Proving it out is much harder.

“My approach has been to urge caution and to do our work in a quiet way and not to hype what we're doing and to let the data speak for itself, because the field has a mixed reputation, and for good reason,” said Verdin, of the Buck Institute. “If you look at our track record as a field, it has not been good so far. But I also predict that we will have a victory in the next five years. And when that victory — like an approved drug — happens, that's going to really open up the public at large to what the real potential is.”

Still, there's more money being injected into the field now and more companies being formed than ever before. And if a victory comes, it will be because people with mature drug development expertise have finally found their way to more basic longevity science, said Tornado's Mannick. “That's what was missing from the field until now,” she said. “A good analogy is probably immuno-oncology, because we're just at the beginning of something that's really going to transform medicine because it's a fundamental risk factor that hasn't been targeted before.”

Over the next decade, that hypothesis is poised to face its most rigorous test. With dozens of clinical trials planned or underway, human data will be arriving that is expected to provide a clearer picture of how well the various approaches for intervening in the aging process actually work.

“The public has to be aware that most of them will fail,” said Kirkland. “But they shouldn’t lose heart. There are bound to be failures because this is a completely new field and those failures are going to be necessary to have a few wins.”

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## ACKNOWLEDGEMENTS

Author: Megan Molteni

Editor: Jason Ukman

Copy editor: Karen Pennar

Art Director: Jennifer Keefe

Designer: Melissa Gomes

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